REMARKS

Claims

Claims 123-152 are pending and stand variously rejected under 35 U.S.C. § 103. As shown above, independent claims 123 and 143 have been amended to make explicit that the fragments used for cloning are isolated as set forth in the claims. Amendment of the claims is not intended to be an acquiescence in the Office's assessment, and Applicants expressly reserve the right to bring the subject matter of the original claims again in a subsequent, related application. No new matter has been added by way of these amendments and the entry thereof is respectfully requested. Thus, claims 123-152 are pending as shown above.

Information Disclosure Statement

Applicants note that the references submitted with the IDS mailed August, 2002 were not received. Although the postcard indicates that the Office received these references, Applicants resubmit copies herewith for the Examiner's convenience. Accordingly, Applicants request consideration of these references and return of the initialed 1449 form submitted in 2002.

Inventorship

On November 21, 2002, Applicants requested a change in inventorship pursuant to 37 C.F.R. § 1.48(b), a copy of which is attached hereto. Applicants herein renew this request and request the changes to inventorship be reflected in an updated filing receipt.

35 U.S.C. § 103

All claims were rejected as allegedly obvious over U.S. Patent No. 5,635,355 (hereinafter "Grosveld" or "the primary reference"), alone or in combination with various secondary references. (Office Action, paragraphs 5-8). In particular, claims 123-128, 130, 135, 143-145 and 147-151 were alleged to be obvious over Grosveld. (Office Action, paragraph 5). Claims 129, 131-133 and 152 were rejected as allegedly obvious over Grosveld in view of the NEB catalog. (Office Action, paragraph 6). Claims 136-142 were rejected as allegedly obvious over Grosveld in view of U.S. Patent No. 5,500,356 (hereinafter "Li"). (Office Action, paragraph 7). Finally, claims 134 and 146 were rejected as allegedly obvious over Grosveld in view of U.S. Patent No. 6,444,421 (hereinafter "Chung"). (Office Action, paragraph 8). In support of all the rejections, it was alleged that Grosveld teaches all elements of these claims except for cloning of DNAseI hypersensitive fragments into a vector. Nonetheless, it was maintained that such cloning would be obvious in view of claim 1, part 1 of Grosveld. *Id.*.

Because the references do not, alone or in combination, teach or suggest the methods of claims 123-152, Applicants traverse the rejections.

Applicants submit that the Examiner has used prohibited hindsight reconstruction in making these rejections, as there is no teaching, suggestion or motivation within any of the cited references to support the rejection made by the Examiner. In addition, the rejections are based on improper picking and choosing of unconnected teachings within the primary reference.

It is axiomatic that the Examiner bears the burden of establishing a *prima facie* case of obviousness. *See, e.g., In re Ryckaert,* 28 USPQ2d 1955, 1956 (Fed. Cir. 1993); and *In re Oetiker,* 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). The reference must teach all the limitations of the claimed invention and, moreover, suggests the desirability of arriving at the claimed subject matter. (*See, e.g., Amgen, Inc. v. Chugai Pharm. Co.,* 18 USPQ2d 1016, 1023 (Fed. Cir. 1991) stating that "hindsight is not a justifiable basis on which to find that the ultimate achievement of a long sought and difficult scientific goal was obvious" and *In re Laskowski,* 10 USPQ2d 1397, 1399 (Fed. Cir. 1989) stating that "the mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification.")

The pending claims are directed to methods of preparing libraries, using specific processes of cloning DNA fragments, as set forth in the first step(s) of the claims. Thus, the claimed methods use only libraries that are prepared by cloning fragments from accessible regions of cellular chromatin, that are isolated as set forth in the claims. There are absolutely no teachings by Grosveld, alone or in combination with the secondary references, which disclose, suggest or provide the motivation to arrive at such methods. Indeed, Grosveld does not teach or suggest preparation of libraries in any way whatsoever. Rather, Grosveld states that hypersensitive sites may be "mapped" (col. 7, lines 59-63). Once mapped, much larger restriction fragments containing these sites are then used for cloning in conjunction with each other and a gene. In other words, unlike the claimed methods, Grosveld in no way teaches or suggests cloning of DNA fragments prepared as described in steps (a) to (d) of claim 123 or steps (a) and (b) of claim 143, to generate libraries of regulatory sequences. Therefore, there is no motivation in Grosveld to clone fragments and prepare libraries as claimed and nothing in this reference that would reasonably lead one of skill in the art to the claimed subject matter.

Moreover, it is plain that Grosveld fails to connect isolation and cloning of the same collection of fragments, as claimed by Applicants. In fact, Grosveld fails to describe isolation of any fragment generated by his analysis of hypersensitive sites. It is well settled that the Office cannot pick and choose from any one reference only so much of it as will support a given

position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art. *In re Wesslau* 47 USPQ 391 (CCPA 1965).

As noted above, there is no suggestion in Grosveld to arrive at the claimed methods, in which fragments from accessible regions of cellular chromatin are selectively isolated and cloned. At best, Grosveld discloses that hypersensitive sites may be mapped. *See, e.g.,* col. 4 and column 8. After mapping, large restriction fragments that include the mapped site within a much larger polynucleotide are isolated. In a completely separate experiment from hypersensitive site mapping, the larger polynucleotides fragments are used for cloning and, in fact, Grosveld teaches that multiple (at least four) large polynucleotides are cloned into the same vector. *See, e.g.,* column 15 of Grosveld. Grosveld does not teach or suggest methods of making libraries as claimed -- there is no nexus set forth in Grosveld between the fragments he obtains by exposure of nuclei to DNase I and cloning of these fragments to generate a library. As stated previously, Grosveld fails to disclose isolation of any fragment generated by DNase I, let alone the cloning of a library of such fragments. Accordingly, the rejection appears to be based on improper picking and choosing of unrelated teachings from this reference and, as such, cannot be sustained.

Turning to the secondary references, Applicants note that, as acknowledged by the Office, none of the secondary references supply what is missing from Grosveld. The NEB catalog teaches particular enzymes with absolutely no reference to how they might be used for making libraries of regulatory sequences. Similarly, Li and Chung are also silent as to methods of preparing regulatory sequence libraries.

In sum, there is no motivation provided by any of the cited references to arrive at methods of preparing libraries or collection of regulatory sequences, as recited in the pending claims. The steps of the claimed methods are precisely defined -- in the claims themselves, not in the references. None of the references teach making libraries containing regulatory sequences according to the claimed methods. Therefore, Applicants respectfully request that the rejection of these claims as allegedly obvious over the cited references be withdrawn, and that these claims be allowed.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the claims are now in condition for allowance and request early notification to that effect.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §1.16, §1.17, and §1.21, which may be required by this paper, or to credit any overpayment, to Deposit Account No. 18-1648, referencing Atty. Docket No. 8325-0015.

Respectfully submitted,

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